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13. ABSTRACT (Maximum 200 words) <p>First annual report on a predoctoral training grant for a social psychology student and former cancer patient intending to work with cancer control and the psychosocial aspects of coping with cancer. Training is supervised and supported by Dr. Gary Morrow and the Behavioral Medicine Unit within the University of Rochester Cancer Center. Areas of training include data acquisition and analysis; interpretation of findings; preparation of research proposals and grants; and writing abstracts, papers, and book chapters. In addition, the training in psychosocial oncology research was augmented by a two-week internship at Stanford University in the techniques of supportive expressive group therapy used by Dr. David Spiegel in the running of his breast cancer support groups. The training also includes the design, implementation and analyses of a randomized controlled experiment examining the relationship between cancer patient expectations for experiencing chemotherapy-induced nausea and vomiting and subsequent symptom development. Eight patients have accrued to the study thus far. The predoctoral training is progressing very well and I anticipate no problems in completing all aspects of it.</p>				
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FOREWORD

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Joseph A. Rowe 6-30-98
PI - Signature Date

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INTRODUCTION

Subject

First annual report on a predoctoral training grant for a social psychology student and former cancer patient intending to work with cancer control and the psychosocial aspects of coping with cancer.

Purpose

The grant provides a stipend as well as research and training funds for three years of supervised training in psychosocial oncology research. This training opportunity combined with my graduate education, my perspective as a cancer survivor, and my experience as a cancer support group leader, is an essential element in my development as a productive researcher. I will be well prepared to meet my personal and career goals of designing and testing interventions to improve the quality of life for cancer patients. The primary focus of my research will be the role that expectations play in affecting cancer patient's response to treatment and development of side effects.

Scope of Research

Training is to be supervised and supported by Dr. Gary Morrow and the Behavioral Medicine Unit within the University of Rochester Cancer Center. Areas of training are to include data acquisition and analysis; interpretation of findings; preparation of research proposals and grants; and writing abstracts, papers, and book chapters. In addition, the training in psychosocial oncology research in the first year of the grant is to be augmented by a two-week internship at Stanford University in the techniques of supportive expressive group therapy used by Dr. David Spiegel in the running of his breast cancer support groups. The predoctoral training is to include the design, implementation and analyses of a randomized controlled experiment examining the relationship between cancer patient expectations for experiencing chemotherapy-induced nausea and vomiting and subsequent symptom development.

It appears that a potentially significant contributor to the continuing prevalence of chemotherapy-related nausea and vomiting (NV) is the patient's own expectation that it will occur. A hypothesis is set forth that an educational intervention for breast cancer patients prior to receiving their first chemotherapy treatment, that is designed to alleviate negative expectations about developing chemotherapy related NV, will reduce subsequent development of treatment related NV. The study currently being conducted is designed to test this hypothesis.

Background

Although advances in antiemetic medications brought about by the introduction of the 5-HT₃ receptor antagonist class of antiemetics (ondansetron, granisetron, tropisetron) have greatly reduced chemotherapy-related vomiting, this has not been the case with treatment-related nausea. Together, the two symptoms remain among the most frequent side effects of cancer chemotherapy.

Vomiting still occurs in approximately 25% of patients and nausea is reported by 78%. Roughly one-third of patients report nausea of moderate or greater intensity.¹ Both symptoms are inherently unpleasant and their prominent role in reducing quality of life has been widely documented.²⁻⁴

Among patients, there is great variation in the frequency and severity of chemotherapy-induced nausea and vomiting (NV) that cannot be accounted for by pharmacologic properties of the chemotherapeutic agents or by known physiologic characteristics of patients. Patients' beliefs and expectations concerning NV development are postulated to account for some of the unexplained variance. These expectations, termed "response expectancies," are distinguished from both "stimulus expectancies" (i.e., anticipation of external consequences such as food, money, praise or punishment) and "intentions" (i.e., anticipation of voluntary response).⁵

Response expectancies have been predictive of symptom report in a number of studies from a variety of experimental perspectives including: recovery from wisdom tooth surgery;⁶ postsurgical pain;⁷ resumption of work, sexual and social activities after coronary artery bypass surgery;⁸ return to work after a myocardial infarction;⁹ and experimentally induced pain.¹⁰⁻¹⁴

Expectations as Predictors of Nausea and Vomiting

Clinical evidence that expectations may be a causal element of nausea and vomiting (NV) comes from a randomized controlled trial testing the efficacy of two chemotherapeutic agents against placebo for the control of gastric cancer.¹⁵ Thirty-five percent of patients in the control arm (n = 130) who were given only an intravenous saline injection at three week intervals for two years reported nausea, 21% had vomiting and 31% had alopecia. Similarly, 8% of subjects given placebo estrogen reported vomiting as a side effect.¹⁶

Researchers examining the relationship between patients' expectations and the development of treatment side effects have reported mixed results. Zook and Yasco¹⁷ indirectly measured expectations for side effect development in 14 patients scheduled to be treated with chemotherapy for the first time by assessing their prior experience with a close friend or relative receiving chemotherapy. The investigators used a 5 item rating scale that ranged from 1 (extremely negative experience) to 5 (extremely positive experience) to categorize these patients' past experience with the person receiving chemotherapy. The responses these 14 soon-to-be-treated patients gave to this measure correlated significantly with their subsequent nausea development ($r = -.67, p > .01$).

Cassileth et al.¹⁸ in a later study directly measured patients' pretreatment expectations for chemotherapy-related NV. They found no significant relationship between responses on their side effect expectancy questionnaire (SE-EXPECT) and later NV in 56 patients receiving chemotherapy for the first time. The questionnaire asked about 16 possible side effects on 5-point rating scales anchored by 1 (I am certain I will not have this) to 5 (I am certain I will have this).

Three later studies used a modified version of the SE-EXPECT scale in examining the relationship between expectations and chemotherapy-induced NV. Contrary to the findings by Cassileth et al., researchers led by Jacobsen¹⁹ found that patients' pretreatment expectations were related to both the frequency and severity of posttreatment nausea in a group of 45 women with breast cancer receiving six weekly chemotherapy treatments. Likewise, Haut, Beckwith, Laurie, and Klatt²⁰ found a significant relationship between expectations and subsequent NV in 36 cancer patients with a variety of malignancies and treatment regimens beginning a first course of chemotherapy. However, the relationship between pretreatment expectations and posttreatment nausea development was not upheld in a later study of 65 patients by Andrykowski and Gregg.²¹

Rhodes and colleagues assessed expectations for NV in 329 patients prior to their first chemotherapy treatment with mixed findings.²² Using Chi-squared analysis, a statistically significant relationship was found between expectations for nausea and nausea development ($p > .05$) but not between expectations for vomiting and subsequent vomiting ($p > .1$). Researchers in another study²³ found a significant relationship between pretreatment expectations for nausea and anticipatory nausea measured prior to the sixth treatment in 59 breast cancer patients receiving chemotherapy. This finding remained significant even after controlling for both the severity and frequency of occurrence of posttreatment nausea ($p > .03$).

Roscoe et al.²⁴ reported on the relationship between response expectancies and symptom development in two companion studies. Expectations for nausea were assessed prior to first treatment in a homogeneous group of 31 subjects with ovarian cancer receiving platinum-containing chemotherapy as hospital inpatients (Study 1), and in 71 subjects with any of a variety of cancer diagnoses treated largely as outpatients (Study 2). Severity of nausea was assessed after patients' first and second treatments (Study 1) and after patients' first and third treatments (Study 2). Each study found a significant relationship between patients' expectations for nausea development measured prior to their first treatment and the mean post-chemotherapy nausea severity averaged across two treatments (all, $p < 0.05$). The relationships remained significant after controlling for emetic potential of the chemotherapeutic agents (Study 1: R^2 change = .153, $p = .03$; Study 2: R^2 change = .116, $p = .004$).

These studies provide evidence that expectancy cognitions play a role in chemotherapy-induced side effect development. They join other psychological constructs, including conditioning^{25, 26} and anxiety^{19, 27} known to affect development of NV symptoms. Expectancies are closely related to these other two factors and may in fact be largely responsible for effects attributed to them. Negative expectancies are an instrumental factor in the development of anxiety.^{28, 29} Likewise, expectancy is thought to play a role in the generation of conditioning effects.^{5, 30, 31} The magnitude of the effect of these psychological factors on NV development is amply demonstrated by the unfortunate fact that approximately 20% of chemotherapy patients experience NV prior to their

treatments.¹ These psychological factors are also thought to contribute to the development and severity of posttreatment symptoms.^{32, 33}

How these response expectancies operate remains largely unknown. Kirsch⁵ suggests that response expectancies account for the placebo effect and are self-confirming. While the biochemical and physiological mechanisms by which placebo effects influence treatment outcome remain largely unclear, it is clear that the effect is substantial and that expectations concerning treatment effectiveness are intimately associated with the process.^{34, 35} A selection of studies involving a manipulation of response expectancies for NV development are described below.

Seasickness was reduced by an expectancy manipulation in an experiment using what the authors termed a "verbal placebo".³⁶ Twenty-five naval cadets were randomly assigned prior to their maiden voyage to either a control condition of non-personalized information or to the experimental condition where each subject was told in confidence that he, based upon his previous psychological and physiological testing, was unlikely to experience as much seasickness as his fellow cadets. This experimental manipulation accounted for 31% of the variance in later reported seasickness ($p > .01$).

The effect caused by a manipulation of patients' expectations for NV development can also be seen in two studies examining the efficacy of acupressure for control of these symptoms. Ferrara-Love, Sekeres, and Bircher³⁷ conducted research on the efficacy of acupressure in reducing NV associated with outpatient surgery. Ninety participants were randomly assigned to receive either standard treatment, standard treatment plus an acupressure wristband, or standard treatment plus a sham acupressure wristband. The wrist bands were placed on the patients in the two treatment groups after surgery. The incidence of NV during the patients stay in the post anesthesiology care unit was significantly different between groups with 10% of the treatment group, 20% of the placebo group, and 50% of the control group reporting symptoms (overall, $p > .001$). While the true acupressure arm participants of this experiment trial did better than those in the sham acupressure arm, indicating the presence of a modest treatment effect, patients in both groups reported substantially lower rates of NV than reported by patients in the control group (all, $p > .01$), thereby indicating the presence of a strong expectancy/placebo effect. Other researchers³⁸ reported similar findings from an experiment using acupressure to control nausea associated with visually-induced motion sickness.

Williams and colleagues³⁹ reported success in reducing NV after major gynecologic operations by means of an expectancy manipulation involving intra-operative taped suggestions played while patients were under full anesthesia. Fifty-one patients were randomized to either the treatment condition of a tape containing positive statements concerning the ongoing surgery and how they would feel upon waking or to the control condition of a blank tape. The incidence of vomiting (32% vs. 69%) and severity of NV (median of 1.5 vs. 5.0; range = 0-10) were significantly less for patients in the treatment condition compared to patients in the control condition (p 's $< .05$).

The studies discussed provide a reasonable rationale for investigating a manipulation of patient expectation by dispelling misconceptions about and building confidence in the efficacy of their antiemetic drug regimen, and examining its potential in enhancing the antiemetic effects of drugs given for the control of chemotherapy-induced NV.

BODY of REPORT

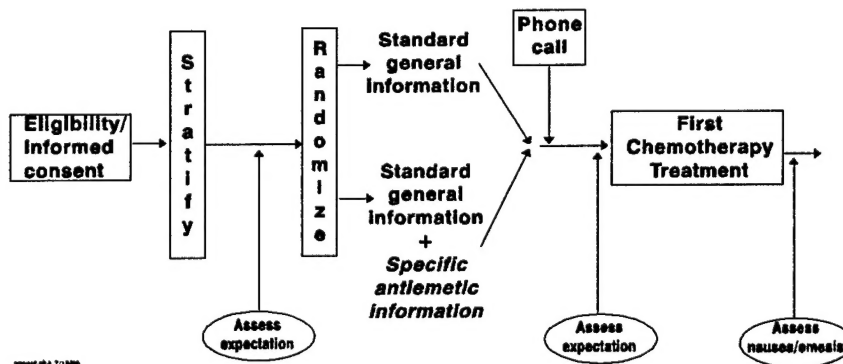
Technical Objectives:

1. To assess the effectiveness of an educational manipulation to affect development of chemotherapy-induced NV as well as to affect patient's expectation for its occurrence.

2. To investigate the relationship between expectations for the development of chemotherapy-related NV and its actual occurrence.

Experimental Methods

Study Design



This is a randomized clinical trial of an education intervention for breast cancer patients prior to their first chemotherapy treatment specifically designed to provide an enhanced positive expectation for efficacy of their antiemetic medication.

Measures

Expectation of Nausea and Other Side Effects. The measure of patient expectation for side effects is based on a questionnaire used previously by Andrykowski,²¹ Jacobsen et al.,¹⁹ and Cassileth et al.¹⁸ Its predictive validity is supported by findings that it significantly predicted subsequent development of nausea. Convergent and divergent validity was supported by further analyses, showing patient expectation of nausea was significantly predictive ($p < .05$) of

future nausea (convergent validity) but that a patient's expectation of any of eleven other specific side effects was not significantly associated with subsequent development of nausea (divergent validity p 's $> .06$). Additional questions examining the patient's expectation for side effects and the expected efficacy of the acustimulation wrist band in controlling NV will be added to the above measure.

Morrow Assessment of Nausea and Emesis (MANE). Nausea and emesis will be measured by the MANE. It has been used by several dozen investigators in studies over the past decade. Psychometric validity and reliability have been reported.^{40, 41}

Delayed Nausea and Delayed Emesis. These are defined as beginning more than 24 hours following completion of chemotherapy with a 24 hour period free of symptoms. They will be measured by a patient report diary developed by Burish⁴² and Carey.²⁶

Statistical Analyses and Assumptions

Outcome variables for this study are: occurrence of nausea and occurrence of vomiting during the first 24 hours after chemotherapy; occurrence of delayed nausea and occurrence of delayed vomiting during days 1-5 after chemotherapy; and change in expectations about nausea and vomiting following the intervention.

A Chi-squared test will be used to test for a difference between the control and intervention groups in the proportions of patients who experience nausea. Similar analyses will be used to compare proportions who experience vomiting, delayed nausea, and delayed vomiting. Logistic regression will be used to determine whether the intervention effect depends on chemotherapy agent, age, sex, or race. In addition, logistic regression will be used to explore the question of whether the intervention influences nausea and vomiting entirely through its effect on expectations. A logistic regression model will be estimated using post-intervention expectation score as a covariate, but not including group assignment (control or intervention). Then group assignment will be added to the model. If it makes a significant contribution to the fit of the model beyond that provided by expectation, this will be evidence that the intervention acts in ways that are not fully captured by the expectation score.

With 36 patients in each of 2 randomized groups, a difference between a control group mean of 2.5 (s.d. = .06) and an experimental group mean of 2.1 (s.d. = .06) can be detected with 80% power by a two sided t -test at $p < 0.05$. These values are clinically relevant differences shown in previous randomized trials using the MANE 5-point scale for nausea severity.

All chemotherapy naive breast cancer patients who are at least 18 years of age or older and able to read English (since the intervention materials will be in a printed format) are eligible for this study.

Procedures

Chemotherapy naive breast cancer patients scheduled to receive adriamycin treatments are stratified by age (under 50 vs. 50 or older) and randomized to one of two arms: Arm 1 = standard educational materials given to new patients; Arm 2 = specific intervention material as well as standard educational materials given to new patients.

The educational material given to all participants include two pamphlets produced by NCI and the ACS to inform patients about chemotherapy side effects and the general effectiveness of antiemetics. The intervention group receive these same materials plus specific information designed to enhance expectations of efficacy by pointing out that ondansetron can control emesis in a majority of patients as well as be effective in the control of nausea. Patients are contacted by study personnel prior to their first chemotherapy appointment to insure that they have read the general information (both groups), read the specific information and answered a brief questionnaire to test whether they have read and understand the specific intervention information (intervention group), and completed the initial expectation measure (both groups). All patients complete the expectation measure both before and after the educational intervention.

All patients receive a standardized dose of ondansetron (Ondansetron 20 mg IV infusion - over 15 min) and Dexamethasone (10 mg IV infusion - over 5-10 min). Patients are studied during the first course of chemotherapy and complete the measure of expectation prior to the intervention. Following the intervention they again fill out the expectation questionnaire (still prior to receiving chemotherapy). Patients complete the MANE and the 5-day diary of posttreatment side effects following treatment.

Results

This training and the research is primarily with my dissertation advisor Dr. Gary Morrow and the Behavioral Medicine Unit within the University of Rochester Cancer Center. Dr. Morrow is an experienced researcher in the area of behavioral and psychological interventions for cancer patients. His recent projects include working with Dr. David Spiegel on a follow-up study to the ground breaking breast cancer support group study done at Stanford.⁴³ They are currently collaborating on a support group intervention study for prostate cancer patients. Dr. Morrow has recently received support from the U.S. Army 1995 Breast Cancer Research Program to study fatigue in breast cancer patients. His office also serves as a research base and coordinating center for 18 institutions involved in the University of Rochester Cancer Center Community Clinical Oncology Program (URCCCCOP). The research administered through this research base focuses on practical, generalizable cancer control interventions using both behavioral and pharmacologic methods.

As a member of Dr. Morrow's research team I am actively involved in the day-to-day activities of ongoing psychosocial and physiologic studies. With his assistance I have analyzed the data from four completed research studies and

manage the databases and data input from two others. We have several joint publications including three journal articles, two chapters, and three abstracts published within the last 12 months. Four additional articles have been submitted for publication. I have also taken part in the writing of two research protocols and two grant proposals generated by our office and critically examined three grant proposals and two articles that Dr. Morrow was asked to review.

In June of this year I spent two weeks at Stanford University in the Spiegel Laboratory. I was able to observe Dr. Spiegel work firsthand with a support group and had several conversations with him concerning aspects of psychosocial interventions and research. Dr. Spiegel generously allowed me to analyze data from two of his studies and I will be involved in the writing of an article with his group based upon the findings from one of these analyses.

My proposed randomized controlled experiment examining the relationship between breast cancer patient expectations for experiencing chemotherapy-induced nausea and vomiting and subsequent symptom development has undergone a substantial delay and modification in order to accommodate an unexpected problem. The study, which was to serve as my dissertation study, was approved by my advisor, the hospital institutional review board and the grant reviewers from your institution. Unfortunately, and unexpectedly, the proposal was rejected by the chairman of my social psychology department as unsuitable for a dissertation because it was unlikely to yield new or interesting information. Lengthy negotiations lead to a two prong solution to the problem this presented.

First, in order to meet the obligations of my predoctoral training grant, I have assumed responsibilities for data management, analyses and report writing for a URCCCCOP protocol that also examines the relationship between patient expectations and subsequent symptom development. This is a study I wrote with Dr. Morrow concurrently with writing my dissertation and grant proposals. The URCCCCOP study, which is larger in both scope and size than my grant proposal study, includes all the essential elements (including measures and the information based expectancy manipulation) of the later study. For the sake of this and subsequent reports to your organization, I will be reporting on data from breast cancer patients participating in this larger study. This study began accruing patients in January 1998. There are currently eight breast cancer patients on study and it is anticipated that there will be no problems reaching the target of 72 breast cancer patients as accrual to this study is expected to sharply increase in the near future when the current most active URCCCCOP study closes. No analyses have been done at this point.

Second, my previously proposed dissertation study will be modified to include a stronger expectancy manipulation and an additional control group. The modified proposal will still entail conducting a randomized controlled experiment examining the relationship between cancer patient expectations for experiencing chemotherapy-induced nausea and vomiting and subsequent symptom development. The expectancy manipulation will involve use of an acupuncture

wrist band and information that it has been shown to be effective in reducing NV. The additional control group (using a sham acupressure treatment) is added to the study to control for actual acupressure effects. This revised version of my dissertation proposal has also received approval by the hospital institutional review board. The study is currently underway but will not be reported on herein.

DISCUSSION AND CONCLUSION

The predoctoral training is progressing very well. I am making excellent use of the opportunity afforded by the grant and by Dr. Morrow and look forward to a productive career in psychosocial oncology research. Thank you.

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